PATENT SPECIFICATION

NO DRAWINGS

Inventors: RICHARD MOATS SHEELEY and GEORGE RODGER ALLEN, JR.

1,164,360

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Date of Application and filing Complete Specification: 30 Nov., 1967.

No. 54652/67.

Application made in United States of America (No. 602148) on 16 Dec., 1966.

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Index at acceptance: —**C2** C(1E5K4, 1G5A, 1G5B, 1G6B5, 1H1A2, 1H1A3, 1H1C3, 1J3B, 1J3C2, 1J3C3, 1M1A, 1M1C2, 1M1C3, 1Q1A, 1Q5, 1Q6C, 1Q7A, 1Q8A, 1Q9F1, 1Q9K, 1Q9L, 1Q11D, 1Q11G, 1Q11J, 2A3, 2A5, 2A14, 2D45, 2R15, 2R16, 2R17, 2R18, 3A13C1C, 3A13C10H, B4A1, B4A2, B4D, B4E, B4H, B4M, L1118X, LE195, LE213, LE247, LE25Y, LE255, LE275, LE30Y, LE305, LE32Y, LE322, LE36Y, LE360, LE361, LE652, LE670, LE680, LE79Y, LE790, 18X-195-275, ML170, ML18X, ML189, ML195, ML213, ML215, ML246, ML247, ML25Y, ML250, ML252, ML255, ML275, ML276, ML30Y, ML305

ERRATUM

SPECIFICATION NO. 1,164,360

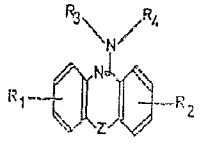
Page 1, For Index at Acceptance **C2C only** read:- (1E5K4, 1G5A, 1G5B, 1G6B5, 1H1A2, 1H1A3, 1H1C3, 1J3B, 1J3C2, 1J3C3, 1M1A, 1M1C2, 1M1C3, 1Q1A, 1Q5, 1Q6C, 1Q7A, 1Q8A, 1Q9F1, 1Q9K, 1Q9L, 1Q11D, 1Q11G, 1Q11J, 2A3, 2A5, 2A14, 2D45, 2R15, 2R16, 2R17, 2R18, 3A13C1C, 3A13C10H, B4A1, B4A2, B4D, B4E, B4H, B4M, 213, 215, 246, 247, 25Y,250, 252, 255, 28X, 30Y, 305, 32Y, 322, 332, 36Y, 360, 361, 621, 652, 670, 671, 680, 681, 708, 79Y, 790, 170-189-276, 18X-195-275, LE, ML)

THE PATENT OFFICE,
10th February 1970

D 121753/7

This invention relates to a method of preparing substituted 11-aminodibenz-[b,f][1,4]oxazepines or thiazepines and substituted 11-aminodibenz[b,f][1,4]diazepines. The products of the method are useful for their (CNS) activity as tranquilizers and anti-depressants as well as analgesics.

The diazepines, oxazepines and thiazepines which may be prepared by the method of this invention may be represented by the following formula:



(I)

wherein R_1 and R_2 are the same or different and each is hydrogen, (C_1—C_6) alkyl, (C_1—C_6) alkoxy, nitro, halogen or trifluoromethyl; R_3 is hydrogen or (C_1—C_6) alkyl; R_4 is hydrogen, (C_1—C_6) alkyl, (C_2—C_6) alkenyl, ω-[di-(C_1—C_6) alkylamino]-(C_1—C_6 alkyl or ω-(hydroxy) (C_1—C_6) alkyl; or —N(R$_3$)(R$_4$) when taken together is

[*Price*

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International Classification:—**C 07 d 57/00; 87/54; 93/42; 99/02**

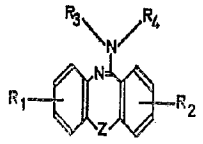
COMPLETE SPECIFICATION

A process for Preparing Tricyclic Organic Compounds

We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a method of preparing substituted 11-aminodibenz-[b,f][1,4]oxazepines or thiazepines and substituted 11-aminodibenz[b,f][1,4]diazepines. The products of the method are useful for their (CNS) activity as tranquilizers and anti-depressants as well as analgesics.

The diazepines, oxazepines and thiazepines which may be prepared by the method of this invention may be represented by the following formula:



(I)

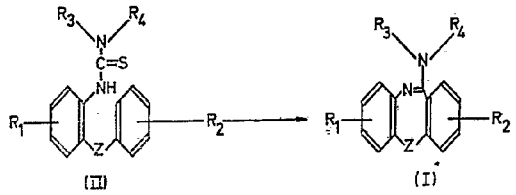
wherein R_1 and R_2 are the same or different and each is hydrogen, (C_1—C_6) alkyl, (C_1—C_6) alkoxy, nitro, halogen or trifluoromethyl; R_3 is hydrogen or (C_1—C_6) alkyl; R_4 is hydrogen, (C_1—C_6) alkyl, (C_2—C_6) alkenyl, ω-[di-(C_1—C_6) alkylamino]-(C_1—C_6 alkyl or ω-(hydroxy) (C_1—C_6) alkyl; or $-N\begin{matrix}R_3\\R_4\end{matrix}$ when taken together is

[*Price*

4-(C_1—C_6) alkyl)-1-piperazinyl, 4-[hydroxy-(C_1—C_6) alkyl]-1-piperazinyl, 4-[dialkylamino-(C_1—C_6) alkyl]-1-piperazinyl, piperidino, morpholino or 2,2-polymethylenehydrazino; and Z is oxygen, sulfur or >N-(C_1—C_6) alkyl.

The compounds with which this invention is concerned are, in general, white crsytalline solids only slightly soluble in water, but moderately soluble in organic solvents such as methanol and ethanol. They are alkaline substances which are usually soluble in aqueous mineral acids at room temperature. They form substantially insoluble acid addition salts such as the hydrochloride, sulfate, phosphate, citrate, tartrate, maleate and fumarate salts. The present compounds, generally in the form of their salts, may be administered orally or parenterally and when so administered are effective central nervous system agents. For oral administration, the compounds prepared by the method of this invention may be incorporated with the usual pharmaceutical excipients and used, for instance, in the form of tablets, capsules, dragees, liquids to be administered in drops, emulsions, suspensions and syrups, and in chocolate, candy and chewing gum. They may also be administered in suppositories, and in aqueous solutions for parenteral injection.

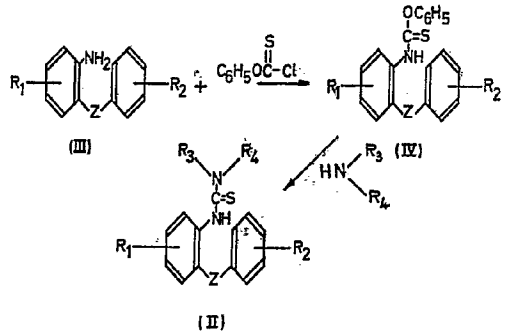
The method of this invention involves the cyclization of substituted thioureas (II) to produce compounds (I) as illustrated by the following reaction scheme:



(III) (I)

wherein R_1, R_2, R_3, R_4 and Z are defined as described hereinabove. The conversion of compounds II into compounds I is achieved by the use of phosphorus oxychloride, optionally, and preferably, in conjunction with phosphorus pentoxide. An excess of the oxychloride may also serve as a suitable solvent. The cyclization reaction is generally carried out at temperatures of from 50°C. to 150°C. with the preferred temperature being from 80°C. to 110°C. The addition of other solvents which are inert under the reaction conditions may also be useful, such as benzene, toluene and xylene. When the cyclization has been achieved, usually after heating from 30 minutes to 24 hours, the products (I) may be recovered by treating the reaction solution with water, followed by purification of the crude product by methods well known to those skilled in the art.

The thioureas (II) which serve as the starting materials for (I) in the method of this invention may be prepared from substituted diphenyl ethers, substituted diphenyl sulfides, and substituted diphenylamines as set forth in the following reaction scheme:



(III) (IV) (II)

wherein R_1, R_2, R_3, R_4 and Z are defined as hereinabove. In accordance with this reaction scheme, acylation of the substituted diphenyl ethers, substituted diphenyl sulfides and substituted diphenylamines with phenoxy thiocarbonyl chloride produces the thiocarbanilates (IV). Treatment of the latter compounds with an appropriate mono or diamine gives the thioureas (II).

The compounds prepared by the method of the present invention are physiologically active on the central nervous system. They show high activity as tranquilizers at non-toxic doses and in some instances anti-depressant properties at dosage levels which produce neither overt stimulation nor depression.

A useful test for tranquilizer activity consists of measuring the reduction of spontaneous motor activity in animals by means of an actophotometer (a photoelectric device for quantitatively measuring locomotor activity). Graded doses of the active compounds prepared by the process of this invention are administered to groups of mice, and the effective dosage range for a significant reduction of motor activity (a measure of tranquilization) compared to control groups is established. The use of reduced motor activity as a measure of tranquilizing activity has been described by W. D. Gray, A. C. Osterberg and C. E. Rauh, Archives Internationales et de Therapie, *Vol. 134*, p. 198 (1961) and W. J. Kinnard and C. J. Carr, Journal of Pharmacology and Experimental Therapeutics, *Vol. 121*, p. 354 (1957).

The anti-depressant properties of the compounds prepared by the method of the present invention are evident by measuring their ability to counteract a depression induced in animals by the administration of tetrabenazine hexamate. Graded doses of the active compounds of this invention are administered to groups of mice, and this is followed by administering a dose of tetrabenazine which is known to markedly depress the exploratory behaviour of normal mice. The anti-depressant treated groups show normal exploratory behaviour, while the control groups, and groups treated with an ineffective anti-depressant agent, do not show this normal exploratory behaviour, but show well known profound depression induced by tetrabenazine. The results from several dose levels are used to establish effective dose ranges. The anti-depressant compounds prepared by the process of this invention show their desirable properties by this procedure at dose levels which produce little or no untoward reactions, such as ataxia or reduced spontaneous motor activity.

In addition, some of the compounds prepared by the method of this invention show other valuable pharmaceutical properties, such as analgesic activity.

The following examples describe in detail the preparation of representative substituted 11-aminodibenz[b,f][1,4]-oxazepines and thiazepines and substituted 11-aminodibenz[b,f][1,4]diazepines by the method of the present invention.

EXAMPLE 1

Preparation of 11-(1-Piperidinyl)dibenz[b,f][1,4]oxazepine

The compound, phenyl *o*-phenoxythiocarbanilate, and piperidine are heated in ethanol at reflux temperature, followed by removal of the solvent and recrystallization of from dilute ethanol. The product obtained is 2′-phenoxypiperidinethiocarboxanilide, melting point 135—136°C.

2′-phenoxypiperidinethiocarboxanilide (1.0 g.) is refluxed with phosphorus pentoxide (approx. 1 g.) in phosphorus oxychloride (5 ml.) for two hours. After cooling to room temperature, the reaction mixture is diluted with ether. The resulting precipitate is washed several times with ether, treated with aqueous potassium carbonate solution (preferably with cooling) and the mixture extracted three times with ether. The ether solution is dried over anhydrous potassium carbonate, and upon evaporation of the solvent, yields a yellow solid which is recrystallized from heptane to give white crystals, melting point 98—100°C.

EXAMPLE 2

Preparation of 11-Aminodibenz[b,f][1,4]oxazepine

Using the procedure described in Example 1, and treating phenyl *o*-phenoxythiocarbanilate with ammoniacal ether produces the product 1-(2-phenoxy)-3-phenylthiourea, melting point 125—127°C., after recrystallization from dilute methanol.

Heating 1-(2-phenoxy)-phenylthiourea, prepared above, with phosphorus pentoxide in phosphorus oxychloride, gives the product as crystals, melting point 198—200°C.

EXAMPLE 3

Preparation of 11-(n-Butylamino)dibenz[b,f][1,4]oxazepine

2-Aminodiphenyl ether hydrochloride (16.66 g., 0.075 mole) is converted into the free base by shaking with dilute ammonium hydroxide. The liberated base is extracted into ether, and the ethereal solution is dried over sodium sulfate. This solution is treated with a solution of 6.45 g. (0.0375 mole) of phenoxythiocarbonyl chloride in ether. The resulting solution is magnetically stirred at ambient temperature for about 21 hours; filtration gives white crystals of 2-aminodiphenyl ether

hydrochloride. The solvent is removed from the filtrate to give an amber oil that crystallizes from hexane to give 12.4 g. of solid, melting point 95—98°C.

A solution of 3.21 g. (10 moles) of phenyl *o*-phenoxythiocarbanilate prepared above, and 1.46 g. (20 moles) of n-butylamine in 50 ml. of ethanol is heated at reflux temperature for 50 minutes. The solvent is removed, and the residue crystallizes on trituration with hexane. Recrystallization of the product 1-butyl-3-(2-phenoxyphenyl)thiourea from ether-hexane gives white crystals, melting point 80—81°C.

In the manner described in Example 1, treatment of 1-butyl-3-(2-phenoxyphenyl)thiourea prepared above, with phosphorus pentoxide in phosphorus oxychloride gives crystals, melting point 67—71°C., after recrystallization from heptane.

EXAMPLE 4

Preparation of 11-(4-Methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

In the manner described in Example 1, treatment of phenyl *o*-phenoxythiocarbanilate with a molar equivalent of 1-methylpiperazine gives the product, 4-methyl-2′-phenoxy-1-piperazinethiocarboxanilide, which forms white crystals, melting point 139—142°C., from dilute ethanol.

Using the procedure described in Example 1, and treating 4-methyl-2′-phenoxypiperazinethiocarboxanilide with phosphorus pentoxide in phosphorus oxychloride gives the above product as crystals, melting point 96—97°C. after recrystallization from heptane.

EXAMPLE 5

Preparation of 2-Chloro 11-[4-(β-Hydroxyethyl)-1-piperazinyl]dibenz[b,f][1,4]oxazepine Dihydrochloride

Using the procedure described in Example 1 and treating phenyl 2-(*p*-chlorophenoxy)thiocarbanilate with 1-(β-hydroxyethyl)piperazine gives the product 2′-(*p*-chlorophenoxy)-4-(2″-hydroxyethyl)-1-piperazinethiocarboxanilide, melting point 155—158°C., after recrystallization from ethyl acetate.

Heating 2′ - (*p* - chlorophenoxy) - 4 - (2″ - hydroxyethyl) - 1 - piperazine - thiocarboxanilide, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product which is dissolved in ether and treated with hydrogen chloride to furnish 2-chloro 11 - [4 - (β - hydroxyethyl) - 1 - piperazinyl] - dibenz[b,f][1,4]oxazepine dihydrochloride as crystals, melting point, 200—232°C.

EXAMPLE 6

Preparation of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine

Using the procedure described in Example 1, and treating phenyl 2-(*p*-chlorophenoxy)thiocarbanilate with 1-methylpiperazine gives crystals of 2′ - (*p* - chloro - phenoxy) - 4 - methyl - 1 - piperazinethiocarboxanilide, melting point 145—147°C., after recrystallization from acetone-hexane.

When the procedure described in Example 1 is used and the starting material is 2′ - (*p* - chlorophenoxy) - 4 - methyl - 1 - piperazinethiocarboxanilide, the product obtained is buff-colored crystals, melting point 109—111°C.

EXAMPLE 7

Preparation of 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]thiazepine

In the manner described in Example 1, treatment of phenyl (*p*-chlorophenylthio)thiocarbanilate with a molar equivalent of 1-methylpiperazine gives the product, 4- methyl - 2′ - (*p* - chlorophenylthio)piperazinethiocarboxanilide hydrochloride.

In the manner described in Example 1, treatment of 4 - methyl - 2′ - (*p* - chlorophenylthio)piperazinethiocarboxanilide hydrochloride, prepared above, with phosphorus pentoxide in phosphorus oxychloride produces white crystals, melting point 114.5—117.0°C., after recrystallization from heptane.

EXAMPLE 8

Preparation of 5-Methyl-11-(4-Methyl-1-piperazinyl)dibenz[b,f][1,4]diazepine

In the manner described in Example 1, treatment of 2-amino-N-methyldiphenylamine with phenoxythiocarbonyl chloride furnishes phenyl 2-(N-methylanilino)-thiocarbanilate, which is obtained as an oil.

In the manner described in Example 1, treatment of phenyl 2-(N-methylanilino)-

thiocarbanilate, prepared above, with 1-methylpiperazine gives crystals, of 4-methyl-2'-(N-methylanilino)-1-piperazinethiocarboxanilide, melting point 131—132°C., after recrystallization from heptane-ethyl acetate.

Using the procedure described in Example 1, treatment of 4 - methyl - 2' - N - methylanilino - 1 - piperazinethiocarboxanilide with phosphorus pentoxide in phosphorus oxychloride gives crystals having melting point 119—120°C. after recrystallization from heptane.

EXAMPLE 9

Preparation of 11-Morpholino-dibenz[b,f][1,4]thiazepine Hydrochloride

In the manner described in Example 1, treatment of 2-aminodiphenyl sulfide with phenoxythiocarbonyl chloride furnishes white crystals, melting point 86—88°C., after recrystallization from ethanol.

Using the procedure described in Example 1, treatment of phenyl 2-(phenylthio)-carbanilate with morpholine in propanol gives crystals of 2' - (phenylthio) - 4 - morpholinethiocarboxanilide, melting point 83—84°C., after recrystallization from ethanol-heptane.

A solution of 300 mg. of 2'-(phenylthio)-4-morpholinethiocarboxanilide in 2 ml. of phosphorus oxychloride containing a drop of dimethylformamide is heated at reflux temperature for 5 hours. The product is isolated in the manner described in Example 1 and is obtained as cream-colored crystals, melting point 250—260°C., after recrystallization from ethyl acetatemethanol.

EXAMPLE 10

Preparation of 11-(2-Dimethylaminoethylamino)dibenz[b,f][1,4]oxazepine

Following the procedure described in Example 1 and treating phenyl *o*-phenoxythiocarbanilate with *unsym*-dimethylethylene diamine in ethanol gives the product, 1 - (2 - dimethylaminoethyl) - 3 - (2 - phenoxy - phenyl)thiourea as a colorless oil.

Heating 1 - (2 - dimethylaminoethyl) - 3 - (2 - phenoxy - phenylthiourea with phosphorus oxychloride in the presence of dimethylformamide at refluxing temperatures produces 11 - (2 - dimethylaminoethylamino)dibenz[b,f][1,4]oxazepine, melting point 82—84°C.

EXAMPLE 11

Preparation of 2-Chloro-11-[(3-dimethylaminoethyl)methylamino]-dibenz [b,f][1,4]thiazepine Hydrochloride

Using the procedure described in Example 1 and treating 2 - (*p* - chlorophenyl - thio)thiocarbanilate with trimethyl ethylenediamine gives the product 1 - [2 - (*p* - chlorophenylthio)phenyl] - 3 - methyl - 3 - (2 - dimethylaminoethyl)thiourea, which is isolated as the hydrochloride salt, melting point 167—168°C.

Heating 1 - [2 - (*p* - chlorophenylthio)phenyl] - 3 - methyl - 3 - (2 - di - methylaminoethyl) thiourea hydrochloride, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product which is dissolved in ether and treated with hydrogen chloride to furnish 2 - chloro - 11 - [(3 - dimethylaminoethyl) methylamino] - dibenz[b,f] [1,4]thiazepine hydrochloride, melting point 196—197°C.

EXAMPLE 12

Preparation of 2-Chloro-11-[4-(3-dimethylaminopropyl)-1-piperazinyl] dibenz[b,f][1,4]oxazepine

In the manner described in Example 1, treatment of phenyl 2-(*p*-chlorophenoxy)-thiocarbanilate with 1-(3-dimethylaminopropyl)piperazine gives an oil that is converted into the dihydrochloride upon treatment with ethereal hydrogen chloride. Crystallization from methanol gives 2' - (*p* - chlorophenoxy) - 4 - (3 - dimethyl - aminopropyl) - 1 - piperazinethiocarboxanilide dihydrochloride, melting point 208—210°C.

Following the process of Example 1, and heating 2' - (*p* - chlorophenoxy) - 4 - (3 - dimethylaminopropyl) - 1 - piperazinethiocarboxanilide dihydrochloride, prepared above, with phosphorus pentoxide in phosphorus oxychloride, the product 2 - chloro - 11 - [4 - (3 - dimethylaminopropyl) - 1 - piperazinyl]dibenz[b,f][1,4] oxazepine is obtained.

EXAMPLE 13

Preparation of 2-Chloro-11-(4-morpholinyl)dibenz[b,f][1,4]thiazepine

Using the procedure described in Example 1 and treating phenyl 2-(*p*-chloro-

phenylthio)thiocarbanilate with morpholine gives the product 2′-(*p*-chlorophenylthio)-4-morpholine-thiocarboxanilide, melting point 65—67°C.

Heating 2′ - (*p* - chlorophenylthio) - 4 - morpholinethiocarboxanilide, prepared above, with phosphorus pentoxide in phorphorus oxychloride gives the product 2-chloro-11-(4-morpholinyl)dibenz[b,f][1,4]thiazepine as crystals, melting point 148—150°C.

EXAMPLE 14

Preparation of 2-Chloro-11-(1-piperidinylamino)dibenz[b,f][1,4]thiazepine

Following the procedure described in Example 1 and treating phenyl 2-(*p*-chlorophenylthio)thiocarbanilate with N-aminopiperidine furnishes the product 1 - [2 - *p* - chlorophenylthio) - phenyl] - 3 - piperidino - thiourea, melting point 158.5—160°C., after recrystallization from ethanol.

Heating 1 - [2 - (*p* - chlorophenylthio)phenyl] - 3 - piperidino - thiourea, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product 2 - chloro - 11 - (1 - piperidinylamino)dibenz[b,f] [1,4]thiazepine as crystals, melting point 153—154°C.

EXAMPLE 15

Preparation or 11-(β-Hydroxyethylamino)dibenz[b,f] [1,4]oxazepine

Using the procedure described in Example 1 and treating phenyl 2-phenoxythiocarbanilate with ethanolamine gives the product 1 - (β - hydroxyethyl) - 3 - (2′ - phenoxy - phenyl)thiourea.

Heating 1 - (β - hydroxyethyl) - 3 - (2′ - phenoxy - phenyl)thiourea, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product 11-(β-hydroxyethylamino)dibenz[b,f] [1,4]oxazepine as crystals, melting point 136—139°C.

EXAMPLE 16

Preparation of 11-(3-Dimethylaminopropyl)dibenz[b,f] [1,4]oxazepine

Following the procedure described in Example 1 and treating phenyl 2-phenoxythiocarbanilate with α-dimethylaminopropylamine furnishes the product 1 - (3 - dimethylaminopropyl) - 3 - (2 - phenoxy - phenyl)thiourea, melting point 113—114°C., after recrystallization from ethanol-heptane.

Heating 1 - (3 - dimethylaminopropyl) - 3 - (2 - phenoxy - phenyl)thiourea, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product as crystals, melting point 108—109°C.

EXAMPLE 17

Preparation of 11-Allylaminodibenz[b,f] [1,4]oxazepine Hydrochloride

Using the procedure described in Example 1 and treating phenyl 2-phenoxythiocarbanilate with allylamine gives the product 1 - allyl - 3 - (2 - phenoxyphenyl) - thiourea as an oil.

Heating 1 - allyl - 3 - (2 - phenoxyphenyl) - thiourea, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product 11-allylaminodibenz[b,f] [1,4]oxazepine, the hydrochloride of which is obtained as crystals, melting point 220°C. with decomposition.

EXAMPLE 18

Preparation of 2-Fluoro-11-(4-methyl-1-piperazinyl)dibenz[b,f] [1,4] oxazepine

Following the procedure described in Example 1, and treating phenyl 2 - (*p* - fluorophenoxy)thiocarbanilate with 1-methylpiperazine furnishes the product 2′ - (*p* - fluorophenoxy) - 4 - methyl - 1 - piperazinethiocarboxanilide.

Heating 2′ - (*p* - fluorophenoxy) - 4 - methyl - 1 - piperazinethiocarboxanilide, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product as crystals, melting point 84—86°C.

EXAMPLE 19

Preparation of 2-Bromo-11-(4-methyl-1-piperazinyl)dibenz [b,f] [1,4]oxazepine

Using the procedure described in Example 1 and treating phenyl 2 - (*p* - bromophenoxy)thiocarbanilate with 1-methylpiperazine gives the product 2′ - (*p* - bromophenoxy) - 4 - methyl - 1 - piperazinethiocarboxanilide.

Heating 2′ - (*p* - bromophenoxy) - 4 - methyl - 1 - piperazinethiocarbox -

anilide, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product as crystals, melting point 95—99°C.

EXAMPLE 20

Preparation of 2-Methyl-11-(4-methyl-1-piperazinyl)dibenz [b,f] [1,4]oxazepine

Following the procedure described in Example 1 and treating phenyl 2 - (*p* - tolyloxy)thiocarbanilate with 1-methylpiperazine furnishes the product 2′ - (*p* - tolyloxy) - 4 - methyl - 1 - piperazinethiocarboxanilide.

Heating 2′ - (*p* - tolyloxy) - 4 - methyl - 1 - piperazinethiocarboxanilide, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product as crystals, melting point 130—131°C.

EXAMPLE 21

Preparation of 8-Chloro-11-(4-methyl-1-piperazinyl)dibenz [b,f] [1,4]oxazepine

Using the procedure described in Example 1 and treating phenyl 5 - chloro - 2 - phenoxythiocarbanilate with 1-methylpiperazine gives the product 5′ - chloro - 2′ - phenoxy - 4 - methyl - 1 - piperazinethiocarboxanilide.

Heating 5′ - chloro - 2′ - phenoxy - 4 - methyl - 1 - piperazinethiocarboxanilide, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product as crystals, melting point 165—166°C.

EXAMPLE 22

Preparation of 6-Chloro-11-(4-methyl-1-piperazinyl)dibenz [b,f] [1,4]oxazepine

Following the procedure described in Example 1 and treating phenyl 3 - chloro - 2 - phenoxythiocarbanilate with 1-methylpiperazine furnishes the product 3′ - chloro - 2′ - phenoxy - 4 - methyl - 1 - piperazinethiocarboxanilide.

Heating 3′ - chloro - 2′ - phenoxy - 4 - methyl - 1 - piperazinethiocarbox - anilide, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product as crystals, melting point 83—87°C.

EXAMPLE 23

Preparation of 4-Chloro-11-(4-methyl-1-piperazinyl)dibenz [b,f] [1,4]oxazepine

Using the procedure described in Example 1 and treating phenyl 2 - (*o* - chlorophenoxy)thiocarbanilate with 1-methylpiperazine gives the product 2′ - (*o* - chlorophenoxy) - 4 - methyl - 1 - piperazinethiocarboxanilide.

Heating 2′ - (*o* - chlorophenoxy) - 4 - methyl - 1 - piperazinethiocarboxanilide, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product as crystals, melting point 173—174°C.

EXAMPLE 24

Preparation of 11-(4-Methyl-1-piperazinyl)-8-trifluoro-methyldibenz [b,f] [1.4]thiazepine Dihydrochloride

Following the procedure described in Example 1 and treating 5 - trifluoro - methyl - 2 - (phenylthio)thiocarbanilate with 1-methylpiperazine furnishes the product 5′ - trifluoromethyl - 2′ - (phenylthio) - 4 - methyl - 1 - piperazinethio - carboxanilide.

Heating 5′ - trifluoromethyl - 2′ - phenylthio - 4 - methyl - 1 - piperazine - thiocarboxanilide, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives the product which is dissolved in ether and treated with hydrogen chloride to furnish 11 - (4 - methyl - 1 - piperazinyl) - 8 - trifluoromethyl - dibenz[b,f] [1,4]thiazepine dihydrochloride as crystals, melting point 192°C. with decomposition.

EXAMPLE 25

Preparation of 2-Methoxy-11-(4-methyl-1-piperidinyl)dibenz [b,f] [1,4]thiazepine

Using the procedure described in Example 1 and treating phenyl 2-(*p*-methoxy-phenylthio)thiocarbanilate with piperidine gives the product 2′ - (*p* - methoxyphenyl - thio) - 1 - piperidinethiocarboxanilide.

Heating 2′ - (*p* - methoxyphenylthio) - 1 - piperidinethiocarboxanilide, pre-

pared above, with phosphorus pentoxide in phosphorus oxychloride gives the product as crystals, melting point 116—117°C.

EXAMPLE 26

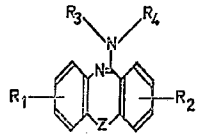
Preparation of 2-Nitro-11-(4-methyl-1-piperazinyl)dibenz [b,f][1,4]oxazepine

1 - Methyl - 4 - piperazinethiocarbonyl chloride, prepared from 1-methyl-piperazine and thiophsogene is treated with *o*-aminophenol to give 1 - methyl - 4 - (*o* - hydroxyphenylthiocarbamoyl)piperazine. This product is treated with 4-chloronitrobenzene in dimethylacetamide in the presence of potassium carbonate. 4 - Methyl - 2′ - (*p* - nitrophenoxy)piperazine thiocarboxanilide is thereby obtained.

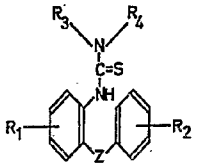
Following the process of Example 1 and treating 4 - methyl - 2′ - (*p* - nitro - phenoxy)piperazinethiocarboxanilide, prepared above, with phosphorus pentoxide in phosphorus oxychloride gives 2 - nitro - 11 - (4 - methyl - 1 - piperazinyl)dibenz [b,f][1,4]oxazepine as crystals, melting point 189—191°C., after recrystallization from hexane.

WHAT WE CLAIM IS:—

1. A method of preparing a compound of the formula:



wherein R_1 and R_2 are the same or different and each is hydrogen, (C_1—C_6) alkyl, (C_1—C_6) alkoxy, nitro, halogen or trifluoromethyl; R_3 is hydrogen or (C_1—C_6) alkyl; R_4 is hydrogen, (C_1—C_6) alkyl, (C_2—C_6) alkenyl, ω-(di-(C_1—C_6 alkylamino)(C_1—C_6) alkyl, or ω-(hydroxy(C_1—C_6) alkyl or —N(R$_3$)(R$_4$) when taken together is 4-[(C_1—C_6) alkyl]-1-piperazinyl, 4-[hydroxy-(C_1—C_6)alkyl]-1-piperazinyl, 4-[dialkylamino (C_1—C_6) alkyl]-1-piperazinyl, piperidino, morpholino, 2,2-polymethylenehydrazino; and Z is oxygen, sulfur or >N-(C_1—C_6) alkyl, the method comprising heating a thiourea of the formula:



wherein R_1, R_2, R_3, R_4 and Z are as defined above, with phosphorus oxychloride, optionally in conjunction with phosphorus pentoxide.

2. A method according to Claim 1, wherein the thiourea is 4 - methyl - 2′ - phenoxypiperazinethiocarboxanilide and the product obtained is 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f][1,4]oxazepine.

3. A method according to Claim 1, wherein the thiourea is 2′ - (*p* - chloro - phenoxy) - 4 - methyl - 1 - piperazinethiocarboxanilide and the product obtained is 2 - chloro - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f][14,]oxazepine.

4. A method according to Claim 1, wherein the thiourea is 4 - methyl - 2′ - (*p* - chlorophenylthio)piperazinethiocarboxanilide and the product obtained is 2 - chloro - 11 - (4 - methyl - 1 - piperazinyl(dibenz[b,f][1,4]thiazepine.

5. A method according to Claim 1, wherein the thiourea is 1 - (2 - dimethyl - aminoethyl) - 3 - (2 - phenoxy - phenyl)thiourea and the product obtained is 11 - (2 - dimethylaminoethyl)dibenz[b,f][1,4]oxazepine.

6. A method according to Claim 1, substantially as described in any one of the Examples herein.

7. A substituted diazepine, oxazepine or thiazepine whenever prepared by a process according to any preceding claim.

8. A pharmaceutical preparation comprising a compound according to Claim 7 together with a pharmaceutically acceptable carrier or diluent.

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